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Translation rewiring at the heart of phenotype switching in melanoma

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Coverage on Falletta et al., (2017) Translation reprogramming is an evolutionarily conserved driver of phenotypic plasticity and therapeutic resistance in melanoma. Genes & Dev. 31,18-33

During tumor progression cancer cells are constantly challenged by intrinsic oncogene-induced and extrinsic micro-environmental stress signals such as hypoxia, nutrient deprivation, oxidative and genotoxic stress. Under these suboptimal growth conditions cancer cells activate an Integrative Stress Response (ISR), which results in a transient

decrease in energy consumption followed by a cellular adaptation phase and possibly recovery, if the environmental conditions become more favorable. Translation is a very high energy-consuming process; it is therefore not surprising that to minimize energy consumption cancer cells turn down global protein synthesis rates while reprograming translation towards specific transcripts required for survival and adaptation.

Selective translation is regulated mostly, but not exclusively, at the translation initiation step. It is achieved by means of specific sequences and/or structures in the transcripts, which are recognized by trans-acting translation factors and/or RBPs (RNA Binding Proteins) in the absence (or limiting amounts) of "canonical" initiation factors. Two common *in cis* motifs that drive selective translation are uORF (Upstream Open Reading Frames) and IRES (Internal ribosome Entry Sites) sequences (Truit and Ruggero, 2016). uORFs are found in genes induced by stress (e.g. ATF4, see below). This motif represses translation of the downstream main ORF in normal growth conditions. IRES, instead, are structural motifs predominantly located in the 5'UTR of stress-response genes. This motif can drive translation in sub-optimal growth conditions; a state that is often associated with a shortage in initiation factors required for CAP-dependent translation (Truit and Ruggero, 2016). uORFs and IRES-dependent translation are both primed by eIF2alpha phosphorylation and inactivation of mTOR, two events triggered by the majority, if not all, stress signals. Both events synergize to reduce CAP-dependent translation, and thus energy consumption, and activate selective translation of transcripts essential for survival and adaptation. A key factor that is preferentially translated in stress conditions to promote adaptation is the transcription factor ATF4, the best characterized effector of the ISR.

Melanoma cells are well-known for their plasticity and ability to phenotype switch between two very distinct cell states, often referred to as the proliferative and invasive cell states. Whereas the transcriptome of the proliferative state is mainly driven by MITF and SOX10 the invasive state, which is reminiscent to a mesenchymal-like cell state characterized by low levels of MITF, increased invasive properties and therapy resistance, is mainly driven by the AP1 and TEAD transcription factors (Verfaille et al., 2015). Although phenotype switching has attracted a lot of attention in the field over the last decade our understanding of the molecular mechanisms underlying this key event remains relatively poor.

In the last issue of Genes and Development, Falletta and colleagues (Falletta et al., 2017) provide evidence that phenotype switching is actually triggered by an ISR-dependent translation reprogramming. The authors report that melanoma cells subjected to prolonged glutamine deprivation and/or to inflammatory stimuli (i.e. TNFalpha exposure), as a means

to mimic stress conditions melanoma cells encounter within their natural tumor microenvironment, suppress MITF while inducing expression of the key mediator of the ISR, ATF4. They also demonstrate that these stimuli inhibit eIF2B, a GEF (Guanidine Exchange Factor) necessary for translation initiation, and thereby inhibit global translation. These data are consistent with a model in which ISR engagement directly promotes MITF down-regulation through both ATF4-dependent silencing of *MITF* transcription and reduced protein synthesis as a consequence of the global decrease in translation rates. Critically, the glutamine starvation gene expression signature (GSS) correlated with the two reference invasive gene expression signatures reported by Hoek in 2008 (Hoek et al., 2008) and Verfaillie in 2015 (Verfaille et al., 2015). Notably, although ATF4 expression in nutrient-rich medium caused a robust decrease in MITF expression it failed to induce a proliferative-to-invasive phenotype switch. In contrast, glutamine deprivation or pharmacological inhibition of eIF2B induced invasiveness, and tumor-initiation capacity, in a series of in vitro and in vivo assays. These data firmly identify ISR-induced inhibition of eIF2B as a crucial driver of melanoma phenotype switching.

Importantly, the authors also provide additional genetic evidence that nutrient limitation-induced translation reprogramming is an evolutionarily conserved driver of invasive behavior all the way down to the budding yeast *Saccharomyces cerevisiae*. All in all, Falletta and colleagues coherently and elegantly integrates in an evolutionary conserved context, microenvironmental cues, metabolite availability and invasive behavior. They propose that melanoma cells behave just like any other normal cell, including a budding yeast, that try to cope/survive in a hostile environment: they stop dividing, save energy and adopt an invasive phenotype in search of a better place to live.

Falletta's work has important clinical implications. They show that the GSS overlaps with targeted- and immune-therapy resistant signatures and therefore propose that targeting translation reprogramming may offer new avenues towards delaying/preventing acquisition of therapy resistance. Instead, targeting CAP-dependent translation may be more detrimental than beneficial as it is expected to potentially promote invasive behaviors. Unfortunately, to date clinically-compatible inhibitors that selectively target uORF and/or IRES-dependent translation have not been identified. The work from Falletta and co-workers therefore warrants the development of such inhibitors and their use in the context of combination therapy. Moreover, these inhibitors might actually even become useful in the context of cancer prevention. A recent paper indeed reported that non-melanoma skin cancer initiation is highly dependent on translation rewiring towards uORFs (Sendoel et al., 2017).

Notably, selective translation can also be driven by a different codon usage due to cancer-specific transcription and/or modifications in the anticodon loop of certain tRNAs. Modification of specific tRNAs, which leads to enhanced translation of various oncogenic proteins, promotes the formation of breast cancer metastases (Delaunay S et al., 2016). Together these findings highlight critical roles for ISR and translation reprogramming in cancer initiation and progression and therapy resistance.

In conclusion, there is an increasing body of evidence implicating selective translation in various aspects of cancer biology. The data point towards translational reprogramming being a common mechanism adopted by cancer cells to survive in their hostile environment, and in particular upon exposure to therapy. Translation reprogramming may therefore be viewed as a new key hallmark of cancer. Importantly, the discovery of cancer-specific vulnerabilities in translational reprogramming is of great interest and may eventually lead to the development of new targets for therapeutic intervention.

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